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Title	1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP): a powerful condensing reagent for phosphate and phosphonate esters
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Graphical Abstract

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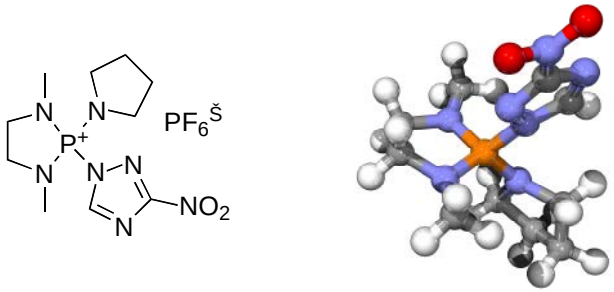
Natsuhisa Oka, Mamoru Shimizu, Kazuhiko Saigo, and Takeshi Wada*



1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP): a powerful condensing reagent for phosphate and phosphonate esters

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Abstract

A novel phosphonium-type condensing reagent, 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP), was designed and synthesized. A ^{31}P NMR study on the condensation reactions of phosphate, alkylphosphonate, boranophosphate, and *H*-phosphonate derivatives with an alcohol in the presence of MNTP demonstrated the versatility and the enhanced activity of the new condensing reagent, compared to the previously reported phosphonium-type condensing reagents. The mechanism of the condensation reactions mediated by MNTP is discussed on the basis of the ^{31}P NMR studies and theoretical calculations.

Key words

Phosphonium-type condensing reagent, Phosphate, Alkylphosphonate, Boranophosphate, *H*-phosphonate

1. Introduction

Phosphate esters, especially those which play important roles in cells such as nucleic acids,[1,2] phosphoinositols,[3,4] phospholipids,[5] sugar phosphates,[5,6] and phosphopeptides,[7] are one class of important targets in current synthetic organic chemistry. The most frequently

used method to synthesize these phosphate esters as well as their analogs is the *O*-phosphitylation with phosphoramidites (the phosphoramidite method),[8-11] because the reactions proceed rapidly and efficiently under mild acidic conditions. However, this method has some shortcomings. Firstly, care should be taken to store the phosphitylating reagents due to their instability to oxidation and hydrolysis. The reactions have to be carried out under strictly anhydrous conditions for the same reason. Secondly, an additional step, such as oxidation, sulfurization, or boronation, to transform the phosphite intermediates into the corresponding phosphate derivatives is required, which may cause some undesired side reactions depending on substrates (e.g., the dealkylation by I^- and/or hydrolysis of substrates during oxidation with I_2/H_2O, the reduction of substrates caused by a boronating reagent, and so on).[12-16]

In the course of our study to develop new synthetic methods for nucleic acid derivatives, we have been devoting much effort to the design and synthesis of condensing reagents for *O*-phosphorylations and *O*-phosphonylations, which have some advantages over the *O*-phosphitylations by the phosphoramidite method and can be appropriately chosen depending on target molecules.[17-19] The advantages are: 1) condensation reactions can be carried out without strictly anhydrous conditions; 2) the phosphorylating and phosphonylating reagents can be stored for a long period of time without being oxidized or hydrolyzed; 3) an additional step, such as oxidation, is eliminated. These characteristics would enable one to synthesize some functionalized molecules, which are difficult to be synthesized by the phosphoramidite method. As such a successful result, we have developed a new boranophosphorylation reaction of nucleosides mediated by a condensing reagent and could synthesize dinucleoside boranophosphates containing four nucleobases,[18,19] which were difficult to be synthesized by the phosphoramidite method due to serious side reactions on the nucleobases caused by a boronating reagent during the boronation of the phosphite intermediates.[13-16] However, *O*-phosphorylations and *O*-phosphonylations (except for the

reaction of reactive *H*-phosphonates) suffer from the low reactivity of the phosphorylating and phosphonylating reagents, compared to that of phosphitylating reagents in the phosphoramidite method. This would be a significant drawback, especially when target molecules require multiple phosphorylations or phosphonylations as the synthesis of DNA/RNA analogs. To remedy this drawback and to develop an efficient condensing reagent applicable to a wide variety of phosphate derivatives, we designed a new phosphonium-type condensing reagent, 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (**1**). In this paper, we report the synthesis of **1** and its application to the synthesis of phosphate and phosphonate esters. The synthesis of **1** and the comparison of the reactivity of **1** with that of the prototype condensing reagent, 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (**2**),[19] are also described in detail.

2. Results and discussion

2.1. Design and synthesis of 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP) and 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP)

Phosphonium-type condensing reagents, which were originally developed for the peptide synthesis,[20-23] have also proven to be effective for the synthesis of phosphate and phosphonate derivatives.[17,19,24-27] For example, 2-(benzotriazol-1-yloxy)-1,3-dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (BOMP) (Figure 1, **3**) was successfully used for the rapid formation of *H*-phosphonate diesters.[17] The study showed that **3** was much more effective for the

activation of *H*-phosphonate monoesters than the parent commercially available condensing reagent, benzotriazol-1-yloxy-2-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP) (Figure 1, **4**).[21] Although **3** is one of the most active condensing reagents at present, we considered that further improvement of the molecular structure would be necessary for the development of a versatile condensing reagent applicable to various phosphate and phosphonate esters. Although the activation of the P-O$^-$ functions of phosphates or phosphonates with **3** would form active intermediates, 1-benzotriazolyl phosphates or phosphonates, they should be much less reactive than activated *H*-phosphonates. Given this situation, we designed 1,3-dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP, **1**), in which 3-nitro-1,2,4-triazole was introduced in the place of 1-hydroxybenzotriazole in **3**, as a new condensing reagent, because the effectiveness of 3-nitro-1,2,4-triazole as a nucleophilic catalyst has already been demonstrated with the prototype condensing reagent, 3-nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP, **2**),[19] and because 3-nitro-1,2,4-trialzole has also been used as an efficient nucleophilic catalyst for *O*-phosphorylations and *O*-phosphonylations with conventional condensing reagents, such as 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT).[28]

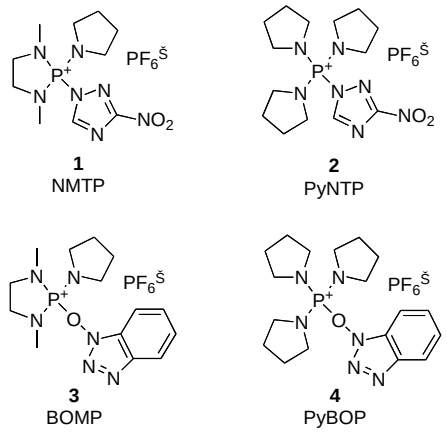
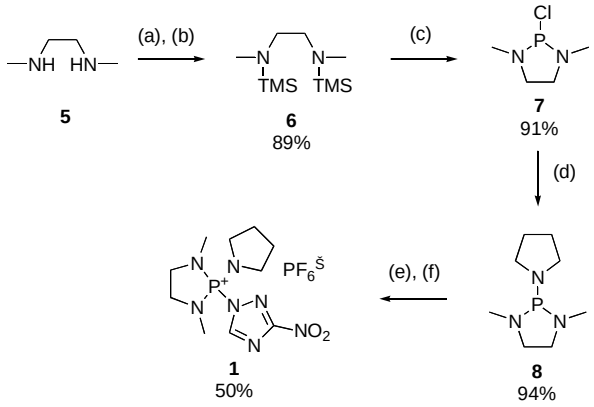


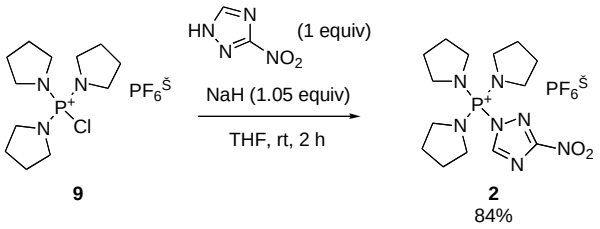
Figure 1. Phosphonium-type condensing reagents.

The synthesis of **1** is outlined in Scheme 1. 1,3-Dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidine (**8**) was prepared from *N*,*N*'-dimethyl-1,2-ethylenediamine (**5**) in 3 steps,[29] and **8** was allowed to react with 3-nitro-1,2,4-triazole in the presence of carbon tetrachloride, followed by a counteranion exchange to give **1** as a colorless crystalline solid, which could be stored in a vial for at least 12 months at -30 ˚C.



Scheme 1. Synthesis of MNTP **1**. *Reagents and conditions*: (a) BuLi (2.1 equiv), Et_2O–hexane, -78 ˚C then 0 ˚C, 30 min; (b) TMSCl (2.1 equiv), -78 ˚C then rt, 2 h; (c) PCl_3 (1 equiv), 0 ˚C then rt, 6 h; (d) 1-(trimethylsilyl)pyrrolidine (1 equiv), 0 ˚C then reflux, 1 h; (e) 3-nitro-1,2,4-triazole (1 equiv), CCl_4 (4 equiv), CH_2Cl_2, -78 ˚C, 1 h then rt, 30 min; (f) KPF_6 (1 equiv), CH_3CN, rt, 1 h.

PyNTP **2** could be synthesized by a much simpler protocol than that for **1** (Scheme 2). The nucleophilic substitution of the chloro group on the phosphorus atom of a commercially available condensing reagent, chlorotri(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyCloP, **9**)[22] with 3-nitro-1,2,4-triazole in the presence of NaH yielded **2** in good yield as a colorless crystalline solid, which could also be stored in a vial for at least 12 months at -30 ˚C.



Scheme 2. Synthesis of PyNTP **2**.

The optimized geometries of **1** and **2** calculated at the HF/6-31G* level showed that **1** was a little less congested around the phosphorus atom, compared to **2** (Figure 2). This reduced steric hindrance of **1** may have some positive effect on the reaction rate mediated by this new condensing reagent.

1 **2**

Figure 2. Optimized geometries of **1** and **2** calculated at the HF/6-31G* level.

2.2. Condensation reactions of dimethyl phosphate in the presence of the phosphonium-type condensing reagents 1 and 2

For the validation of our molecular design of the new phosphonium-type condensing reagent, we chose the condensation of dimethyl phosphate **10a** with 2-phenylethanol **11** as a simple model reaction, and compared the condensation activity of **1** with that of **2** and **3**. The phosphate **10a** was allowed to condense with **11** (1.5 equiv) in the presence of **1**, **2** or **3** (3 equiv) and a weak, less nucleophilic base, 2,6-lutidine (10 equiv), as an acid scavenger in CH_3CN–CD_3CN (4:1, v/v) at 20 ˚C, and the reactions were monitored by ^{31}P NMR. The results clearly demonstrated the superiority of **1** and **2** over **3** with respect to the reaction rate (Figure 3). Thus, the desired phosphate triester **12a** was formed in 98 and 83% yields after

150 min when **1** and **2** were used, respectively. In the former case, **12a** was isolated in 98% yield after the usual work-up and purification by silica gel column chromatography. On the other hand, only 33% of **12a** was generated within the same time period, when **3** was used.

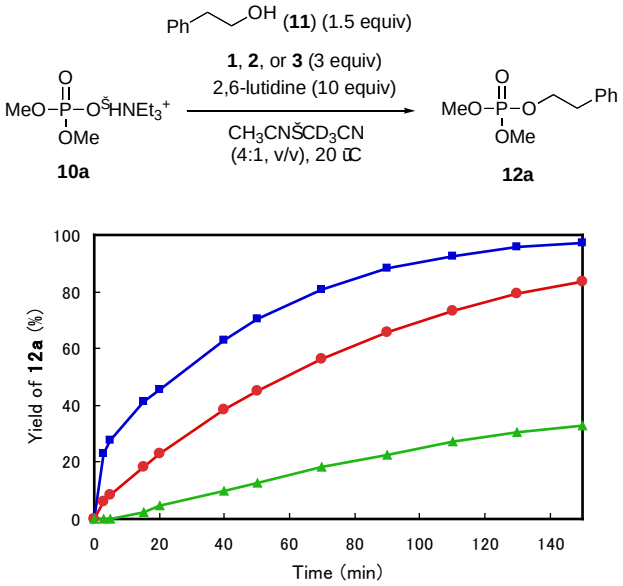


Figure 3. Condensation reactions of dimethyl phosphate **10a** with 2-phenylethanol **11** (1.5 equiv) in the presence of **1**, **2**, or **3** (3 equiv) in CH_3CN–CD_3CN (4:1, v/v) at 20 ˚C. ■, MNTP **1**; ●, PyNTP **2**; ▲, BOMP **3**.

The condensation reaction of **10a** with **11** mediated by **1-3** is most likely to start with the generation of the active intermediate **13a**,**b** (Figure 4). This type of active intermediates have also been proposed for the PyBOP-mediated activation of phosphonates.[25] There are some possible pathways from **13a**,**b** to the final product **12a**. The pathway via the symmetric pyrophosphate **14a** (path *a*) undoubtedly exists; the generation of **14a** and its conversion to the final product **12a** could be monitored by ^{31}P NMR (**14a**, δ -9.6;[30] **12a**, δ 1.9, Figure 5).[31] In the presence of **1** or **2**, the rate-determining step of the path *a* must be the reaction of **14a** with 3-nitro-1,2,4-triazole (Nt–H) judging from the fact that **14a** was the only intermediate

observed by ^{31}P NMR. However, there is not only one pathway, because the reaction rate was affected by the phosphonium skeleton of the condensing reagents (Figure 4, **1** vs. **2**), which is not involved in the rate-determining step of the path *a*. Our assumption is that there are two other pathways, the paths *b* and *c* shown in Figure 4, and the rate constants of the nucleophilic attacks of X–H (path *b*) and **11** (path *c*) at the electronically neutral phosphorus atom of **13a** are larger than at that of **13b**. Then, we carried out the *ab initio* molecular orbital calculations (HF/6-31G* level) for **13a**,**b** to find that the energy levels of the unoccupied molecular orbitals (UMOs) of **13a** were lower in general than those of **13b**.[32] For example, the energy level of the lowest UMO (LUMO) of **13a** was calculated to be 38.7 kcal/mol, whereas that of **13b** was 46.3 kcal/mol. The structures of **1** and **2** may also affect the rate of the nucleophilic attack of **10a** at the electronically neutral phosphorus atoms of **13a**,**b** (path *a*). However, we consider that the paths *b* and *c*, which should originally have larger activating energy values than the path *a*, would be relatively more affected than the path *a*.

The slow reaction mediated by **3** would be attributed to the less reactive benzotriazol-1-yloxy ester **15b** generated from **10a** and **3**.[33] In fact, the intermediate **15b** was observed throughout the reaction by ^{31}P NMR monitoring (δ 1.4) and gradually consumed to yield **12a**,[32] whereas the reactive intermediate **15a** could not be detected by ^{31}P NMR.

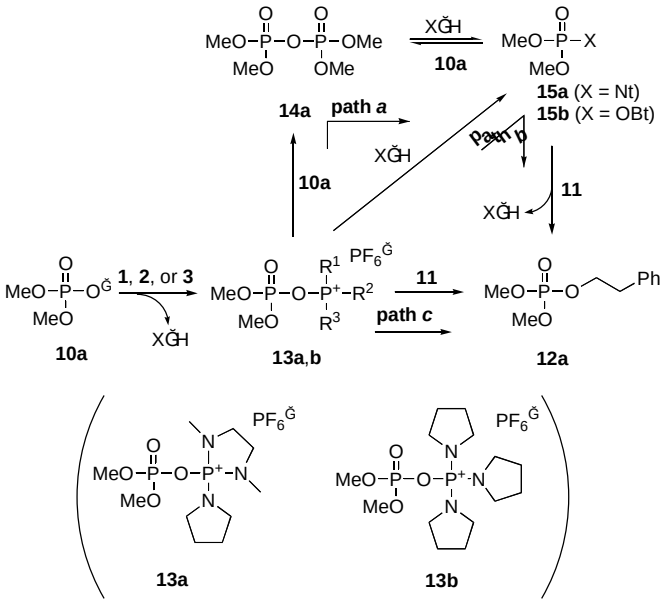
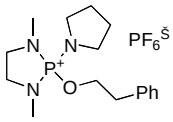


Figure 4. Possible reaction pathways for the reaction of **10a** with **11** in the presence of **1**, **2**, or **3**. X–H = Nt–H = 3-nitro-1,2,4-triazole for **1** and **2**; X–H = BtO–H = 1-hydroxybenzotriazole for **3**.

It should be noted that there was a by-product when **1** was used for the condensation reaction of **10a** with **11**. A ^{31}P NMR analysis showed a signal at δ 34.9 (Figure 5), which was assigned to that of **16** by the independent reaction of **1** with **11**. This side reaction was rather unexpected, because the nucleophilic attack of alcohols to a positively charged phosphorus atom assisted by a weak base, such as 2,6-lutidine, is known to be slow.[17,19,25] In fact, this side reaction was not observed when **2** or **3** was used.[34] The ratio of **16** increased upon using a stronger base; the ratios for **12a** and **16** upon completely consuming **14a** were 45:55 with *N*,*N*,*N*',*N*'-tetramethyl-1,8-naphthalenediamine and 48:52 with triethylamine, while 79:21 with 2,6-lutidine. This result suggests that the condensation of less reactive phosphates with sterically less hindered alcohols should be carried out using more than one molar equivalent of the alcohols in the absence of a strong base.



16

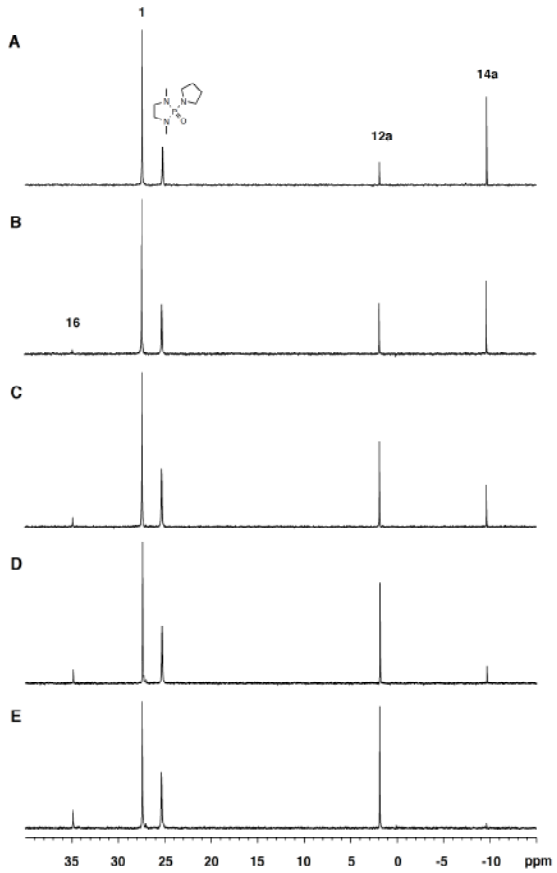


Figure 5. ^{31}P NMR spectra of the reaction mixture obtained by the reaction of **10a** with **11** (1.5 equiv) in the presence of **1** (3 equiv) in CH_3CN–CD_3CN (4:1, v/v) at 20 ˚C. (A) 3 min; (B) 20 min; (C) 50 min; (D) 90 min; (E) 150 min.

2.3. Application of MNTP to various phosphate and phosphonate esters

In the next stage, the condensation reactions of various phosphate and phosphonate derivatives with **11** were carried out in the presence of **1**. ^{31}P NMR monitoring studies demonstrated that **1** was more effective for the condensation reactions of **10b**-**d** with **11** than for the reaction of **10a** with **11** (Figure 6). Thus, all of the reactions of **10b**-**d** with **11** were completed within 40 min; especially **10c** and **10d** were completely condensed within 3 min and 10 min, respectively. As a result, **12b** and **12c** were isolated in 99 and >99% yields. The quantitative formation of **12d** was confirmed by the ^{31}P NMR spectrum, which showed a newly generated signal at 10.6 ppm with a P-H coupling typical of dialkyl *H*-phosphonates

($^{1}J_{PH}$ = 691.3 Hz).[32] In the cases of **10b-d**, any undesired byproducts including **16** were not observed by ^{31}P NMR within the period for the quantitative formation of **12b-d**.[32]

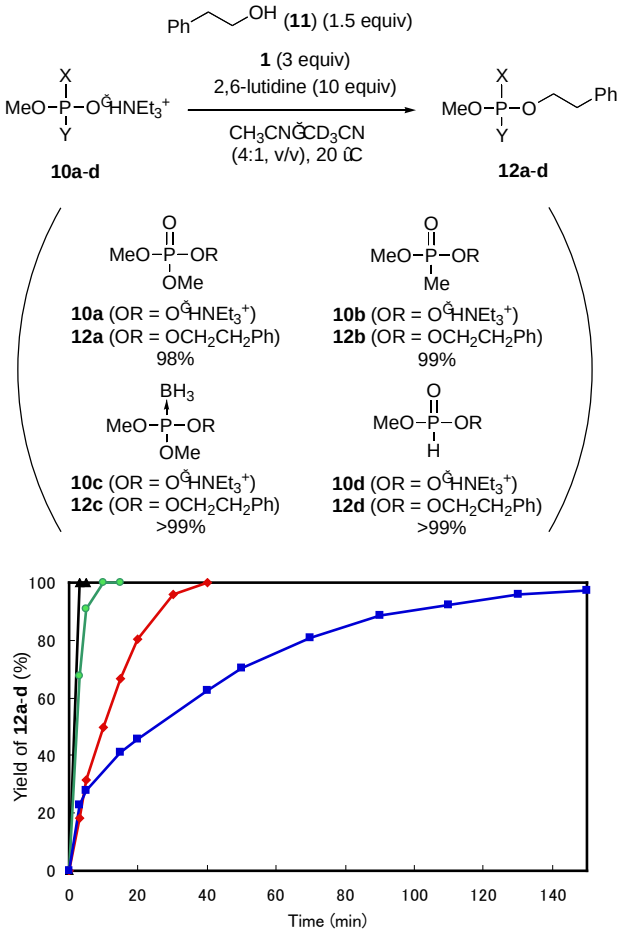


Figure 6. Condensation reactions of **10a-d** with **11** (1.5 equiv) in the presence of **1** (3 equiv) in CH_3CN-CD_3CN (4:1, v/v) at 20 ˚C. ■, **10a**; ◆, **10b**; ●, **10c**; ▲, **10d**.

3. Conclusion

MNTP has proven to be a powerful condensing reagent, which mediated the rapid formation of various phosphate and phosphonate esters. Such versatility and enhanced activity of MNTP would reduce the problem of slow and inefficient reactions in the phosphorylation and phosphonylation of alcohols mediated by conventional condensing reagents and make these methods comparable to the phosphitylation by the phosphoramidite method. MNTP and its simpler counterpart PyNTP were found to be good alternatives to the

phosphoramidite method, especially for the synthesis of various functionalized phosphate derivatives, which are difficult to be synthesized by the phosphoramidite method. In addition to the synthesis of phosphate derivatives, the new phosphonium-type condensing reagents presented in this paper may also be useful for the rapid assembly of polypeptides as well as carboxylic acid esters, considering the wide-use of phosphonium-type condensing reagents for this purpose.

4. Experimental

4.1. General Information

^{1}H NMR spectra were obtained at 300 MHz with tetramethylsilane (TMS) as an internal standard in $CDCl_3$ or CD_3CN. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as an internal standard (δ 77.0) in $CDCl_3$, or with CD_3CN as an internal standard (δ 117.8) in CD_3CN. ^{31}P NMR spectra were obtained at 121 MHz with 85% H_3PO_4 as an external standard in $CDCl_3$ or CD_3CN. Melting points were uncorrected. Silica gel column chromatography was carried out using silica gel 60N (63-210 μm). Organic solvents were purified and dried by appropriate procedures. Isolated phosphate and phosphonate derivatives (**12a-c**) were determined to be >95% pure by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies.

4.2. *Ab Initio* Calculations

Ab initio molecular orbital calculations were carried out using the Gaussian 03[35] and Spartan '04[36] programs on a Dell Precision 650 workstation. Geometry optimizations were carried out at the HF/6-31G* level.

4.3. 1,3-Dimethyl-2-(3-nitro-1,2,4-triazol-1-yl)-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (MNTP, 1)

1,3-Dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidine **8** (14.2 g, 76 mmol) was added dropwise over 2 h to a stirred solution of 3-nitro-1,2,4-triazole (8.67 g, 76 mmol), which was dried by repeated coevaporations with dry pyridine and dry toluene, and dry CCl_4 (29.3 mL,

304 mmol) in dry CH_2Cl_2 (150 mL) at -78 ˚C under argon. The mixture was then allowed to warm to rt and concentrated to dryness under argon. The residue was dissolved in dry CH_3CN (75 mL), and a solution of KPF_6 (14.0 g, 76 mmol) in dry CH_3CN (210 mL) was added dropwise over 1 h to the solution with stirring at rt under argon. The resultant white insoluble solid was removed by suction filtration, and the filtrate was concentrated to dryness. AcOEt (400 mL) was added to the residue, and the insoluble solid was collected by suction filtration, washed with AcOEt (50 mL), and dried under vacuum to afford **1** as a colorless crystalline solid (16.9 g, 38 mmol, 50%). Mp. 175-177 ˚C (decomp.). IR (KBr) 3135, 2990, 2898, 1568, 1511, 1280, 1145, 829, 580, 558 cm^{-1}. ^1H NMR (300 MHz, CD_3CN) δ 8.85 (s, 1H), 3.62-3.33 (m, 8H), 2.89 (J_{PH} = 11.7 Hz, 6H), 2.06 (m, 4H). ^{13}C NMR (75 MHz, CD_3CN) δ 166.2, 153.1 (d, J_{PC} = 7.5 Hz), 49.6, 47.5 (d, J_{PC} = 15.0 Hz), 31.6 (d, J_{PC} = 4.5 Hz), 27.0 (d, J_{PC} = 9.0 Hz). ^{31}P NMR (121 MHz, CD_3CN) δ 25.0, -144.9 (septet, J_{PF} = 701.8 Hz). Anal. Calcd for $C_{10}H_{19}F_6N_7O_2P_2$: C, 26.98; H, 4.30; N, 22.02. Found: C, 26.77; H, 4.40; N, 21.87.

4.4. 3-Nitro-1,2,4-triazol-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyNTP) 2

To powdery NaH (0.254 g, 10.5 mmol), prepared from NaH dispersion in mineral oil prior to use, was added a solution of 3-nitro-1,2,4-triazole (1.14 g, 10 mmol), which was dried by repeated coevaporations with dry pyridine and dry toluene, in dry THF (40 mL) at rt under argon. The mixture was then added a solution of PyClop (**9**) (4.22 g, 10 mmol) in dry THF (10 mL) at rt, and the mixture was stirred for 2 h. The insoluble solid was filtered off and thoroughly washed with dry CH_2Cl_2 (ca. 50 mL). The combined filtrate was concentrated under reduced pressure to some extent (ca. 20 mL) and cooled to 0 ˚C. The resultant precipitate was collected by suction filtration, washed with a small amount of THF, and dried under vacuum to afford **2** (4.19 g, 8.4 mmol, 84%) as a colorless crystals. Mp. 161-163 ˚C (decomp.). IR (KBr) 3118, 2984, 2880, 1566, 1510, 1285, 1143, 854, 590, 557 cm^{-1}. ^1H NMR (300 MHz, CD_3CN) δ 8.79 (s, 1H), 3.40 (m, 12H), 2.03 (m, 12H). ^{13}C NMR (75 MHz,

CD_3CN) δ 165.5, 151.7 (d, J_{PC} = 8.3 Hz), 49.0 (d, J_{PC} = 4.9 Hz), 26.5 (d, J_{PC} = 9.2 Hz). ^{31}P NMR (121 MHz, CD_3CN) δ 19.3, -142.5 (septet, J_{PF} = 698.8 Hz). Anal. Calcd for $C_{14}H_{25}F_6N_7O_2P_2$: C, 33.67; H, 5.05; N, 19.64. Found: C, 33.76; H, 5.03; N, 19.58.

4.5. ^{31}P NMR monitoring of the condensation reactions of dimethyl phosphate or its analogs (10a-d) with 2-phenylethanol 11 in the presence of the phosphonium-type condensing reagents

150 μmol of **1**, **2**, or **3** was placed in an NMR sample tube and dried under vacuum over P_2O_5. Dry CD_3CN (100 μL), an anhydrous CH_3CN solution of triethylammonium dimethyl phosphate (**10a**) or one of its analogs (**10b**-**d**) (50 μmol), which was dried by repeated coevaporations with dry CH_3CN (400 μL), dry 2-phenylethanol (**11**) (9.0 μL, 75 μmol), and distilled 2,6-lutidine (58.2 μL, 500 μmol) were added. The sample tube was then sealed, shaken to dissolve the condensing reagent. After 1.5 min, the ^{31}P NMR data accumulation was started. Each accumulation was carried out over 1.5 min at every time-point of 3, 5, 15, 20, 40, 50, 70, 90, 110, 130, and 150 min (Figures 3 and 6).

4.6. Dimethyl 2-phenylethyl phosphate 12a

After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with a 1 M HCl aqueous solution (3 × 3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were washed with a saturated NaCl aqueous solution (2 × 3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane/ethyl acetate (1/1, v/v)] to afford **12a** (11.3 mg, 49 μmol, 98%) as a colorless oil. ^1H, ^{13}C, and ^{31}P NMR spectra were identical to those reported in the literature.[37]

4.7. Methyl 2-phenylethyl methylphosphonate 12b

After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with 0.2 M phosphate buffer (pH 7) (3 × 3 mL). The combined aqueous layers were

back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane/ethyl acetate (1/1, v/v)] to afford **12b** (10.6 mg, 49 μmol, 99%) as a colorless oil. IR (film) 3444, 2956, 1645, 1497, 1455, 1313, 1231, 1016, 912, 818, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 4.23 (m, 2H), 3.61 (d, J_{PH} = 11.1 Hz, 3H), 2.98 (t, J = 6.9 Hz, 2H), 1.38 (d, J_{PH} = 17.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 128.9, 128.4, 126.6, 66.1 (d, J_{PC} = 6.3 Hz), 37.1 (d, J_{PC} = 6.3 Hz), 11.4, 9.5. ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.0. FAB-HRMS: *m*/*z* calcd for $C_{10}H_{15}O_3P$ (M^+) 214.0759, found 214.0752.

4.8. Dimethyl 2-phenylethyl boranophosphate 12c

After the ^{31}P NMR experiment, the reaction mixture was diluted with CH_2Cl_2 (3 mL), washed with 0.2 M phosphate buffer (pH 7) (3 × 3 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography [hexane/ethyl acetate (4/1, v/v)] to afford **12c** (11.4 mg, 50 μmol, quant) as a colorless oil. IR (film) 2955, 2396, 1455, 1260, 1028, 798, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 4.20 (q, J = 7.1 Hz, 2H), 3.61 (d, J_{PH} = 11.1 Hz, 6H), 2.98 (t, J = 7.1 Hz, 2H), 0.42 (brq, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.8, 128.3, 126.5, 67.1 (d, J_{PC} = 3.4 Hz), 52.9 (d, J_{PC} = 3.5 Hz), 36.8 (d, J_{PC} = 5.5 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 117.7 (q, J_{PB} = 99.1 Hz). FAB-HRMS: *m*/*z* calcd for $C_{10}H_{18}BO_3P$ (M^+) 228.1089, found 228.1094.

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Supplementary data

^{31}P NMR spectra of the reaction mixtures obtained by the reaction of **10a** with **11** in the presence of **2** or **3**; ^{31}P NMR spectra of the reaction mixtures obtained by the reaction of **10b**,**c**, or **d** with **11** in the presence of **1**; ^{1}H, ^{13}C, and ^{31}P NMR spectra of **1**, **2**, and **12b**,**c**. Experimental details for the synthesis of **6**-**8**. Optimized geometries and the orbital energies of the reaction intermediates **13a**,**b**.

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Footnotes

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